REMARKS

I. Status of the Claims

Claims 26 and 30-50 are pending in the application, claims 1-25 and 27-29 having been canceled. Claims 30-50 are withdrawn, and thus claim 26 is under examination and stands rejected under 35 U.S.C. §112, first paragraph and under 35 U.S.C. §102 over Dorken *et al.* The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claim 26 remains is rejected as allegedly lacking an adequate written description and enablement for sequences 70% homologous to SEQ ID NO. 1 which retain the function of binding to CD19. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to remove the homology recitation. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Rejection Under 35 U.S.C. §102

Claim 26 remains rejected as anticipated by Dorken *et al.*, U.S. Patent 7,112,324. The examiner argues that Dorken provides for "single-chain multifunctional polypeptides comprising at least two binding sites specific for the CD19 and CD3 antigen" It is further argued that "the limitation [of] ... no more than 5% of the total weight ..." is met by Dorken's disclosure of standard purification techniques such as imidazole gradient, gel filtration, cation exchange chromatography, and gel electrophoresis. Once again. Applicants traverse.

In their previous response, applicants argued that a careful reading of the description of Example 6 of Dorken provides that purity of the column fractions was examined under

denaturing conditions. "Purity of column fractions was assessed by ***reducing*** sodium dodecyl sulfate (SDS Bis/Tris 4-12 % polyacrylamide gradient gel electrophoresis (PAGE) employing a MOPS buffer system (Novex)" (emphasis added; page 25, line 51-54). However, if one were to follow the specific teachings of Example 6 of Dorken, multimeric and monomeric bispecific antibody constructs ***cannot be distinguished*** for the simple reason that the multimeric proteins would have all been dissociated into monomeric proteins. Thus, the results of this assay are meaningless when assessing what percentage of multimer exists. The examiner has again repeated her reliance on Figs. 11 and 14 of the reference, revealing the same flawed understanding of the reference's teachings.

It was further noted that in the present application, ratios of the polypeptide in monomeric/multimeric form were determined by a combination of SDS-PAGE performed under reducing conditions, Western Blot performed using Penta-His (Qiagen) and Goat-anti-mouse-AP (Sigma) antibodies and gel filtration performed on a Sephadex S200 column. The relative proportions of bispecific single chain polypeptide present in dimeric form are shown in Table 1. As can clearly be seen, each bispecific single chain antibody with anti-human CD3 antigen binding specificity, including SEQ ID NO. 1, spontaneously forms significant amounts of multimeric (*i.e.*, here, dimeric) species when left uncontrolled. The propensity to spontaneously form homodimers therefore appears to be a generic characteristic of the class of the bispecific single chain antibodies examined. Thus, this evidence indicates that Dorken's composition would have a far higher than 5% multimeric protein content, and certainly more than the revised claims which now state 3% content.

The examiner has not accepted these argument for at least two reasons. First, inexplicably, the examiner states on page 5 of the action that "the instant claim is drafted in the

product-by-process format." This is absolutely false, as there are no process limitations in claim 26. While applicants may have argued, and properly so, that the methods that produce such compositions are indeed novel and non-obvious, that is not the same thing as advancing an actual product-by-process claim. As such, this statement must be dismissed out of hand.

The only other reason offered by the examiner in rebuttal is that Dorken discloses "several methods of purifying the bispecific antibody construct," and that these generic disclosures (listed above) by Dorken overlap with techniques described in the instant application. Thus, it is stated that although Dorken does "not describe the production of the molecule using the methods identical to that ... recited in the claim, Dorken discloses the [that] polypeptides of the present invention can be purified according to standard procedures of the art including column chromatography as described in the instant application." Nothing could be more false.

As the examiner readily admits, Dorken is silent on the issue of percentage multimer in the final composition. This is critical because the claims are drawn to a ***composition***, not a "molecule" (polypeptide). Because Dorken lacks such an explicit teaching, this rejection can ***only*** be advanced based on a theory of inherency. As will be explained below, the required elements for advancing an inherency rejection – which are significant – are not found here.

"The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the

claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Also, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure ***at the time of invention***, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. §102 and §103. However, the examiner ***must*** provide a rationale or adduce evidence tending to show inherency. In this regard, the fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of

the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

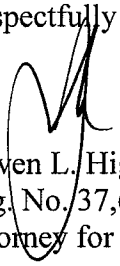
Now, returning to Dorken, the issue here is not whether the methodologies mentioned in Dorken may be similar to those in the present application, but whether the teachings of Dorken would inevitably and necessarily lead to the ***composition*** of claim 26. As has already been pointed out, the Dorken data upon which the examiner is relying utilized ***reducing*** conditions, meaning that ***all*** multimers were rendered ***monomeric***, thus providing ***no*** evidentiary assistance to the examiner's argument. Moreover, only through the use of the ***particular*** methods of the present invention can one achieve the presently claimed compositions – mere generic mention of standard purification techniques are ***not*** sufficient to shift the burden to applicants to rebut an allegation of inherency. And even if they were, the data mentioned above regarding spontaneous multimer formation would do just that, namely, prove that Dorken did ***not*** produce an anticipatory composition. The attached declaration from inventor Dr. Thomas Urbig further confirms each of these facts.

In light of the foregoing information, it is clear that the procedures described in Dorken's Examples do not accurately represent the amount of multimer in their composition. Moreover, the absence of any disclosure in Dorken of the ratio now specified in claim 26 means that the examiner must satisfy the rigorous requirements of an "inherency" rejection, and that has not been done. To the contrary, the claimed compositions are only obtained by the inventive processes of the present invention whereby the skilled artisan is able to separate the monomeric and multimeric forms of the bispecific antibody constructs and to obtain the mixture with the claimed multimer ratio. As such, claim 26 is not anticipated by Dorken. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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